*Микроэлементы в медицине 9 (3—4): 21—24*

ПРОБЛЕМНАЯ СТАТЬЯ

# MECHANISM OF APOPTOSIS FROM THE POSITION OF BIOINORGANIC CHEMISTRY

# МЕХАНИЗМ АПОПТОЗА С ПОЗИЦИЙ БИОНЕОРГАНИЧЕСКОЙ ХИМИИ

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KEYWORDS: apoptosis, phenylphosphonium cations, calcium, zinc

КЛЮЧЕВЫЕ СЛОВА: апоптоз, фенилфосфониевые катионы, кальций, цинк

ABSTRACT: Achievements in bioinorganic chemistry have allowed new insight on the mechanisms of occurrence and development of severe diseases, for example apoptosis. Its mechanism shows fundamental laws of interdependency of elements. These laws propose the mechanism of chain reaction in a basis of diseases. The majority of scientists agree with a genetic nature of ageing, and the initial reason of self-destruction of cells is accumulation of free radicals in cellular organelles. We believe that genetic and biochemical mechanisms are secondary. «The programmed destruction» of cells actually reflects change of stages of chain reaction of apoptosis.

РЕЗЮМЕ: Достижения бионеорганической химии позволили по-новому рассмотреть механизмы возникновения и развития тяжелых заболеваний, в частности явление апоптоза. Его механизм отражает фундаментальные законы взаимодействия химических элементов. Эти законы предполагают, что в основе заболеваний лежит механизм цепной реакции. Большинство ученых согласны с тем, что старение имеет генетическую природу и причиной самоуничтожения клеток является накопление свободных радикалов в клеточных органеллах. Мы считаем, что генетические и биохимические механизмы вторичны. «Программированная смерть» клеток в действительности отражает смену стадий в цепной реакции апоптоза.

The problem of apoptosis now causes a heightened interest of experts of different scientific disciplines: bioinorganic chemistry, biochemistry, molecular biology and genetics, oncology, gerontology and pharmacology. Activation of apoptosis explain course of a cancer, AIDS, diseases of the locomotor apparatus and nervous system, Parkinson's, Alzheimer's and Wilson's diseases. Probably, on the mechanism of apoptosis cells die off at an ischemia of a brain and an insult, and at anaemia. Therefore, finding — out of the mechanism of apoptosis has paramount value for a modern science. Management of processes of apoptosis, on the one hand, can significantly lower death rate from the listed diseases, and with another — increase life span.

A. Kerr and coauthors entered the term in 1972 for phenomenon of programmed destruction of cells with the characteristic cascade of molecular and morphological processes (Harmon et al., 1998). Apoptosis can be caused by different reasons — external (poisons) and internal (activation of «genes of death» or the «programmed» participation of different receptors and enzymes) (Belushkina, Beletskij, 2004).

Concerning the mechanism of process of unanimity, it is not observed. For example, minimum 6 theories of the ageing explaining the reasons of apoptosis are known. Four imply the basic genetic factors, and two — infringement of a power metabolism (Longo et al., 2005).

Variety of these theories assumes, that the starting mechanism of apoptosis is «struggle» of cells against free radicals («active forms of oxygen», «reactive oxygen species», ROS) in the mitochondria (Skulachev, 2001). This implies, that stimulation of antioxidizing system (AOS), or addition of antioxidants in cells should

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interfere with processes of apoptosis and increase life span by the termination of «genetically programmed suicide» (Skulachev, 2005).

According to the «antioxidizing» hypothesis, screening of antioxidants in organelles of cells was carried out. It was found out, that the most active are phenylphosphonium cations (PPC). For the best permeability through hydrophobic structures of cell walls and membranes of mitochondria to tetraphenylphosphonium cation, the decanyl hydrophobic «tail» was attached. This substance has received the name «Skulachev's ion» (SkQ). It has delocalized a positive charge and is «super strong» antioxidant (Fig. 1).

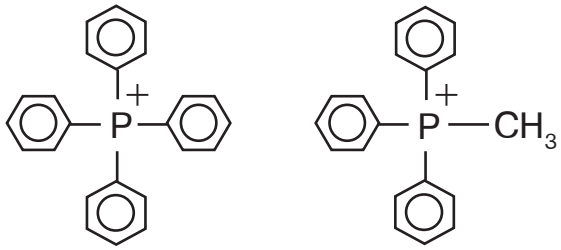


***Fig. 1.*** *Tetraphenylphosphonium (tetraPP) and metylthreephosphonium (TPMP) cations*

PPC easily penetrates into cells and accumulates in negatively charged matrix of mitochondria (Hekimi, Guarente, 2003), presumably, by the physical law of an attraction of heteronomy charges. In 26 October, 2006 on 1st Scientific Festival of the Lomonosov Moscow State University V.P. Skulachev informed, that preliminary experiences of addition SkQ in a diet of mice showed positive results on increase of average duration of their life. Dropping of 20 nM of SkQ solution in a cornea of several kinds of animals with eye diseases have shown amazing effect on improvement of visual acuity, in some cases resulted in enlightenment of blind animal (dogs, cats, the horse), after two—three weeks of treatment. Positive pharmacological action of SkQ has explained activation of antioxidizing system (AOS) and neutralization of free radicals inside of mitochondria.

Surprisingly, authors of theories of ageing ignore the known facts of antagonistic influence of different elements, for example, $Ca^{2+}$ and $Zn^{2+}$ ions, on processes of apoptosis. These ions are named by their role in a metabolism, accordingly, «the main inorganic messenger» and «the main inorganic hormone» (Williams, Frausto da Silva, 1997). Laws of interaction of elements since 1950 are studied within the framework of bioinorganic chemistry. Basic laws of behaviour of metals in a metabolism are formulated.

From this point of view, an explanation of the above-described effects is another. Activation of AOS and neutralization of ROS are secondary, and the reason is in the field of laws of interdependent of elements. Among them the basic are the law of replacement and its consequence, which take into account a basis of cybernetics — a principle of feedback, and a rule of a fractional threshold.

In conformity with the first consequence of the law of replacement, «free» Ca supersedes ions of transition metals from complexes with proteins and nucleoproteins, breaking their functioning and causing polymicroelementose. Surplus of $Ca^{2+}$ supersedes $Mg^{2+}$, inactivates all exchange processes connected with ATP. First it causes decrease of activity of the sodium pump and, hence, of membrane potential ($\psi$) and dependent on it processes of neutralization of free radicals.

It is known that the basic enzymes of antioxidizing system (catalase, peroxidase, cytochrome oxidase, glutathione peroxidase) are located n the structure of haem with ionic complex formed by Fe and Cu, selenoproteins with Se and I. In conformity with the second consequence of the law of replacement, surplus of $Ca^{2+}$ in cytoplasm automatically results in sharp reduction of antioxidizing activity.

Chain reaction, formation of a free radical in each atom with uncoupled electron, begins. The circuit of transformations of the present substances produces molecules, more reaction able, than valentsaturated initial molecules. In addition, processes of apoptosis are shown first from infringement of activity of membranes.

«Free» $Ca^{2+}$ is cytotoxic, and therefore plays a key role in initial stages of development of apoptosis. Its concentration in cells is always increased; it is the initiator of chain reaction. Activated endonuclease, which splits DNA in internal sites of nucleosomes, and transglutaminase, which covalently connects proteins to a membrane isopeptidic bonds, pervert activity of membranes.

$Zn^{2+}$, according to the law of replacement, reduces concentration of Ca in cells and, hence, postpones the beginning of apoptosis. Therefore, it is inhibitor of this process, in particular, suppressing activity endonuclease and transglutaminase. Delay of process of destruction of cells at receipt of $Zn^{2+}$ shows that the content of «free» $Ca^{2+}$ in cytoplasm of cells decreases, and activity of AOS grows.

Any influence which reduces fraction of «free» $Ca^{2+}$ in cells and organelles will, possibly, slow down processes of ageing and render positive pharmacological effect in the diseases accompanied with accumulation of this fraction: diseases of eyes, osteoporosis, progeria, and Down disease.

The mechanism of chain reaction is well known. Characteristic for this reaction is it multistage character. Circuits can be not ramified when on each spent active particle one is necessary again formed, or ram-

ified, RCR when on one spent active particle it is necessary two and more again formed.

RCR can occur in a stationary mode when speed of a branching is less than speed of destruction of active particles, and in non-stationary, when their destruction occurs more slowly, than a branching. In this case, speed of reaction grows after an exponent and is limited only by an expenditure of initial substances. Transition from stationary to a non-stationary mode occurs in steps at change of concentration of one of initial substances («explosion»).

Feature of chain reactions is the phenomenon's of very effective change even their orientations at insignificant impurity of the substances, capable to remove from system a active particle, that is inhibitors. On such mechanism, multistage and slowly at the first stages, process of apoptosis develops. In essence, this process is usual microelementose. For this reason known antioxidants (for example, vitamins E and C) do not render essential influence on processes of apoptosis as influence not the reason of chain reaction, and on its consequence.

P(III) in SkQ, being complex formed, repeatedly it is not capable to change the valence, that it is completely necessary for process of carry of electrons, an event in AOS. At the same time it is known, that P(V), formed at oxidation P(III), is a component of oxygen acids, in particular a phosphoric acid which easily contacts $Ca^{2+}$, forming triphosphate $Ca_3(P_3O_{10})_2$.The anion with five-valent phosphorus in this connection is sequestrating agent, the formed salt is steady, that disable $Ca^{2+}$ from «free» fraction. Thus, from the point of view of bioinorganic ion SkQ is the effective supplier of active phosphorus for neutralization of surplus «free» $Ca^{2+}$ Ion SkQ, as well as $Zn^{2+}$, is inhibitor chain reaction of apoptosis, but with other mechanism of action. Antioxidizing properties SkQ are of secondary importance.

The described mechanism of apoptosis explains the fact of prolongation of life of the Atlantic salmon at infection of gills larva is a bivalve mollusc white shell *Margarititera margarititera.* These larva's is amplified absorb «free» $Ca^{2+}$, that is in this case they are sequestrating agent in chain reaction of polymicroelementose.

There exists very strict homeostasis of calcium. Many components of systems which support its concentration on a low level (below 10-5M), in particular, system from calcitriol, parathormone and calcitonin (Murray et al., 1988; Marshall, 1995; Koolman, Rohm, 1997) are known.

With ageing, apparently, these mechanisms of the control and functioning are weakened for the different reasons, internal and external. Thus, the begun process of microelementose, depending on genetic and ecological factors, turns in polymicroelementose on the mechanism of chain reaction (Fig. 2).

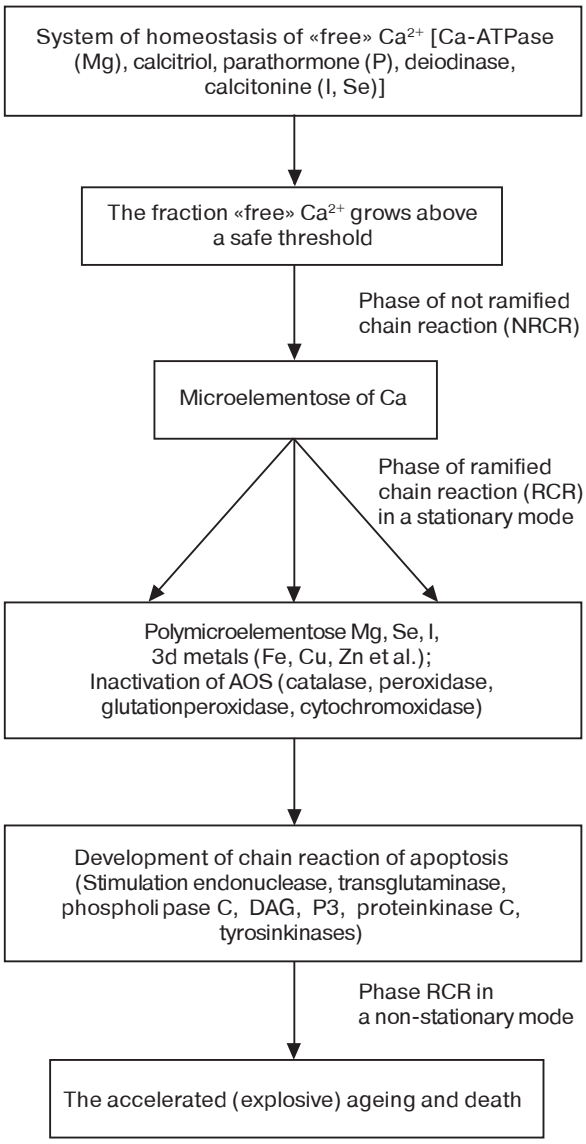


***Fig. 2.*** *The probable mechanism of apoptosis*

Apparently, development of some diseases occurs by mechanism similar to that of chain reaction according to rule of a fractional threshold. The specific displays peculiar to the given pathology can be observed. For example, infringement of Cu homeostasis because of lack of ceruloplasmin results in Wilson's disease, accumulation of Al in temporal lobes of brain (the bottom horns of lateral ventricle of cerebrum) — to Alzheimer's disease (Gladkikh, Sernov, 2002), infringement of homeostasis of Fe in hemosiderin fraction — to haemochromatosis, and so on.

Study of bioinorganic mechanisms of different diseases is perspective for investigation of complex connections of metals and ligands, capable to interact with initiators of chain reactions, and, finally, for development of medicines — inhibitors of these reactions.

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